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Ventilatory Response to Exercise in Patients With Left-to-right Shunts

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An increased ventilatory drive is intimately related to dyspnœa in most forms of heart disease (Campbell and Howell, 1963); knowledge of the mechanisms leading to an excessive ventilatory response is germane to the understanding of the pathogenesis of symptoms in such patients.

In previous communications we have discussed ventilation at rest and on exercise in relation to hæmodynamics and blood chemical changes, in normal subjects (Davies, Gazetopoulos, and Oliver, 1965), in several types of heart disease with closed cardiac septa (Gazetopoulos *et al.*, 1966b; Gazetopoulos, Davies, and Deuchar, 1966a), and in cyanotic congenital heart disease (Davies and Gazetopoulos, 1965). Similar studies in patients with left-to-right shunts remain to be described, the hæmodynamic changes with exercise having already been reported (Davies and Gazetopoulos, 1966). The relation between ventilation, arterial and venous blood chemistry, and hæmodynamics at rest and on effort, is discussed in this paper.

Subjects and Methods

The 34 patients included in this study had communications between the systemic and pulmonary circulations leading to the presence of a left-to-right shunt. The clinical data are presented in Table I. The techniques used for hæmodynamic measurement have been described in the previous paper (Davies and Gazetopoulos, 1966), and the account will, therefore, not be repeated. Ventilation was measured by means of a Wright respirometer at rest and during steady state after the fifth minute of exercise, the values being corrected to B.T.P.S. In parallel with the hæmodynamic and ventilatory measurements, arterial and venous blood samples were obtained in the third-to-fourth and eighth-to-tenth minutes of effort. These blood samples were analysed for *p*H, P_{CO_2}, and bicarbonate content. Lactate and pyruvate determinations were made on arterial blood. These techniques have been previously described (Davies and Gazetopoulos, 1965).

In 10 patients we have studied the effects of heavier exercise on a bicycle ergometer in the sitting position. In 7 of these, rest and exercise data had also been obtained during cardiac catheterization in the supine position; in the other 3, such data had been obtained only at rest. Exercise was begun at low exercise load (200 kpm./min.) and was increased where possible by 200 kpm./min. each 10 minutes, usually to the maximum exercise tolerance. Measurements of oxygen uptake, ventilation, heart rate, and arterial blood chemistry were made in similar sequence to that outlined above. The techniques employed for studies in the upright position have been the same as in normal subjects (Davies *et al.*, 1965) and in patients with other forms of heart disease (Gazetopoulos *et al.*, 1966a).

Results

Mild Supine Exercise. Table I shows the ventilatory response at rest and on exercise in the supine position (hæmodynamic data have been given in the previous paper, the cases and their designations being the same). Table II shows the arterial and venous blood chemistry in those patients in whom measurements were made.

Ventilation and Hæmodynamics. Figure 1 illustrates the ventilation in relation to the oxygen consumption, the types of lesion being designated by different symbols; the limits of normality are those taken from the published material and our data from this laboratory (Gazetopoulos *et al.*, 1966b). Excessive ventilation is seen in a number of patients. Three showed slight arterial desaturation on effort due to an associated small right-to-left shunt: their ventilatory response did not appear to be unusual on this account.

In Fig. 2 we have plotted the deviation of ventilation from the mean normal for the given oxygen

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TABLE I

CLINICAL DATA, OXYGEN UPTAKE, VENTILATION, VENTILATORY EQUIVALENT, AND RESPIRATION RATE AT REST AND ON EXERCISE DURING CARDIAC CATHETERIZATION

Case No., sex, and age			B.S.A. (m.²)	Hb (g./100ml.)	Diagnosis	Clinical disability	Oxygen uptake ml.²/min.(STPD)		Ventilation l./min.(BTPS)		Ventilatory equivalent		Resp. rate	
							Rest	Exerc.	Rest	Exerc.	Rest	Exerc.	Rest	Exerc.
AN 1	M	14	1·65	13·7	ASD	1	240	520	5·5	16·0	2·3	3·1	12	18
AN 2	F	38	1·60	13·3	ASD	2	200	370	10·8	12·3	5·3	3·1	28	28
AN 3	F	30	1·70	14·4	ASD	3A	170	420	5·5	12·6	3·2	3·0	20	23
AN 4	F	16	1·50	11·5	ASD	1	160	470	4·1	10·0	2·6	2·1	14	16
AH 5	F	24	1·50	14·8	ASD	1	190	450	6·0	13·7	3·2	3·1	20	30
AN 6	F	28	1·60	11·6	ASD	1	250	390	6·0	10·0	2·4	2·6	16	18
AN 7	F	34	1·60	12·9	ASD	2	140	330	6·9	17·8	4·9	5·4	21	25
AN 8	F	51	1·80	14·0	ASD	2	230	—	9·6	—	4·2	—	22	—
AH 38	M	52	2·10	15·3	ASD, PH	3A	190	790	6·8	21·2	3·6	2·7	15	20
AH 39	F	59	1·90	12·8	ASD, PH AF	2	270	410	7·1	11·9	2·6	2·9	17	24
AH 40	F	59	1·50	13·3	ASD, PH	2	180	450	5·6	13·4	3·1	3·0	19	21
AH 41	M	54	1·90	16·7	ASD, PH AF	3A	180	760	4·3	17·7	2·4	2·3	13	15
AH 42	M	48	1·80	16·4	ASD, PH	3A	200	870	8·8	25·6	4·4	3·0	18	24
AH 43	F	31	1·35	10·6	ASD, PH	3A	220	600	7·3	14·9	3·3	2·5	25	26
AH 44	F	39	1·60	13·1	ASD. PH	3B	200	370	6·6	12·9	3·3	3·5	15	26
AH 45	F	49	1·70	15·9	ASD, PH MS, AF	3A	180	400	4·4	15·9	2·5	3·9	20	28
AS 82	M	22	1·90	13·9	ASD, PS	1	280	590	7·5	19·5	2·7	3·3	17	20
AS 83	F	9	0·90	12·6	ASD, PS	2	130	230	4·4	9·9	3·4	4·2	20	30
VN 1	M	14	1·60	14·0	VSD	2	250	800	6·5	21·3	2·6	2·7	14	17
VN 2	M	16	1·50	13·6	VSD	1	180	780	5·0	11·0	2·8	1·5	15	23
VN 3	M	37	1·80	14·7	VSD	1	240	620	5·3	16·9	2·2	2·7	16	22
VN 4	F	15	1·50	12·8	VSD	1	170	610	4·8	18·2	2·8	3·0	19	26
VN 5	M	15	1·40	11·8	VSD	1	230	440	6·9	12·5	3·9	2·9	25	32
VH 31	M	26	1·80	15·0	VSD, PH	1	280	670	6·6	17·2	2·4	2·6	15	26
VH 32	M	17	1·50	15·3	VSD, PH	2	200	530	5·3	13·9	2·6	2·6	16	21
VH 33	M	18	1·60	15·8	VSD, PH	2	230	470	6·7	14·5	2·9	3·1	18	22
VH 34	M	62	1·80	17·2	VSD, PH AF	3B	220	—	8·4	—	3·8	—	15	—
VE 62	F	19	1·60	12·3	VSD, PH	3A	210	550	7·0	15·5	3·3	2·8	14	20
VS 81	M	23	1·90	15·8	VSD, PS	1	250	560	6·6	12·0	2·6	2·1	15	20
VS 82	M	19	1·70	15·6	VSD, PS	2	250	660	7·0	17·6	2·8	2·7	15	22
VS 83	M	29	1·80	15·1	VSD, PS	2	210	—	6·2	—	3·0	—	14	—
PN 1	M	10	1·20	11·7	PDA	1	160	450	4·1	12·5	2·6	2·8	15	17
PH 30	F	21	1·30	13·4	PDA, PH	2	180	320	6·6	14·3	3·7	4·5	30	36
PE 65	F	34	1·60	15·1	PDA, PH	2	160	610	5·5	18·9	3·4	3·1	18	21

ASD, atrial septal defect; VSD, ventricular septal defect; MS, mitral stenosis; PS, pulmonary stenosis; PH, pulmonary hypertension; AF, atrial fibrillation; PDA, patent ductus arteriosus.
STPD, standard temperature (37°C.), pressure (760 mm. Hg), dry; BTPS, body temperature and pressure, saturated with water vapour. Clinical disability according to New York Heart Association (1953); Grade 3 divided into 3 A and 3 B after Donald, Bishop, and Wade (1954).

uptake against the pulmonary arterial pressure. Some degree of hyperventilation was present in most patients irrespective of the pressure. Similar results are seen when excess ventilation is related to the magnitude of the pulmonary flow or to the left-to-right shunt.

Figure 3 shows the deviation of exercise ventilation from normal against the degree of impairment of cardiac output, i.e. deviation from mean predicted value for the given oxygen uptake (Gazetopoulos *et al.*, 1966b). It appears that the systemic flow is not a determinant of hyperventilation.

No single hæmodynamic parameter is thus associated clearly with the tendency to hyperventilate, which is seen in most of these patients. Other parameters such as pulmonary vascular resistance and the product of pulmonary arterial pressure and flow were examined, but again no close relationship with ventilation was found. It must be noted that these observations apply to low exercise loads in the supine position.

Ventilation and Arterial and Venous Blood Chemistry. Figures 4 and 5 show the arterial P_{CO_2} and *p*H, measured in the second half of exercise, plotted against the excess ventilation. A number of patients is seen to be hypocapnic, in accordance with their tendency to hyperventilate. Despite this, the *p*H in most cases fell owing to lactic acidæmia. Fig. 6 shows the arterial lactate concentration and the excess ventilation: there is some suggestion that the patients with the higher lactates tend to have a greater ventilation, but the relation is not significant ($p > 0{\cdot}1$).

Figures 7 and 8 deal with the blood gases on the venous side of the circulation. Fig. 7 illustrates the excess ventilation and the pulmonary arterial *p*H. No relation is seen. In Fig. 8 we have plotted the pulmonary arterial P_{CO_2} and the minute ventilation. The broken line represents a normal ventilation—mixed venous P_{CO_2} curve taken from Riley *et al.* (1963). In the same figure we have plotted the findings in other forms of heart disease

TABLE II

BLOOD CHEMISTRY AT REST AND ON EXERCISE DURING CARDIAC CATHETERIZATION

Case No.		Arterial blood						Pulmonary arterial blood			
		So_2	*p*H	Pco_2 (mm.Hg)	Bicarb. (mEq/l.)	Lactate (mM/l.)	Pyruvate (mM/l.)	So_2	*p*H	Pco_2 (mm.Hg)	Bicarb. (mEq/l.)
AN 1	R	97·8	7·420	33·0	21·5	1·23	0·11	88·5	7·405	35·0	21·5
	E	—	—	—	—	—	—	—	—	—	—
		97·1	7·410	35·0	22·0	1·76	0·12	80·8	7·380	38·0	22·0
AN 4	R	95·0	—	—	—	—	—	87·6	7·360	45·0	23·0
	E	—	—	—	—	—	—	69·5	7·340	58·0	23·0
		94·9	—	—	—	—	—	71·0	7·350	56·0	24·5
AN 5	R	95·1	7·415	42·0	25·0	0·85	0·07	90·0	7·400	42·0	24·5
	E	—	—	—	—	1·11	0·08	—	—	—	—
		94·8	7·395	41·0	24·0	1·26	0·08	83·6	7·375	45·0	24·0
AN 6	R	96·0	7·405	32·5	22·0	0·65	0·07	89·0	7·405	34·5	22·5
	E	97·0	7·425	33·0	23·0	0·72	0·07	85·0	7·415	32·0	21·5
		97·1	7·410	36·5	23·0	0·78	0·10	87·5	7·410	37·0	23·0
AH 38	R	93·4	7·350	36·0	20·0	0·91	0·06	81·9	7·345	39·9	20·0
	E	92·9	7·350	36·0	20·0	1·24	0·07	71·0	3·330	40·0	19·5
		89·1	7·350	34·0	19·5	1·30	0·09	63·7	7·330	40·0	19·5
AH 39	R	96·0	7·425	48·0	28·5	0·52	0·07	86·4	7·415	49·0	26·5
	E	—	7·430	40·0	25·5	0·72	0·10	76·5	7·425	46·0	27·0
		94·5	7·430	41·0	26·0	0·98	0·09	79·6	7·415	52·0	27·0
AH 40	R	94·6	7·360	—	—	1·04	0·13	87·5	—	—	—
	E	92·2	7·355	—	—	1·76	—	78·0	—	—	—
		94·6	—	—	—	2·80	—	80·7	—	—	—
AH 41	R	95·9	7·380	39·5	22·5	0·72	0·11	83·2	7·365	44·0	23·5
	E	92·1	7·375	39·5	22·5	1·30	0·12	70·7	7·365	46·0	22·0
		92·1	7·330	41·0	22·5	1·89	0·14	73·0	7·345	48·0	22·0
AH 42	R	91·6	7·390	35·0	22·4	1·04	0·08	82·5	7·370	38·0	21·0
	E	93·7	7·400	31·0	21·0	2·20	0·12	71·4	7·370	38·0	20·5
		90·0	7·370	34·5	20·5	2·14	0·13	71·7	7·365	38·5	20·5
AH 43	R	92·6	7·415	35·0	23·0	0·78	0·06	86·5	—	—	—
	E	89·8	7·370	37·5	21·0	2·14	0·12	75·6	—	—	—
		88·1	7·345	37·5	20·0	2·90	0·16	76·7	—	—	—
AH 45	R	93·7	7·390	38·0	23·0	0·98	0·09	87·0	7·380	40·0	22·5
	E	—	—	—	—	—	—	—	—	—	—
		95·1	7·390	37·5	23·0	1·89	0·10	87·0	7·345	40·5	21·0
VN 2	R	98·4	7·400	40·0	24·0	—	—	78·0	7·395	40·0	24.0
	E	—	—	—	—	—	—	—	—	—	—
		95·6	—	—	—	—	—	68·3	7·370	40·0	22·5
VN 3	R	94·3	—	—	—	—	—	81·0	7·370	52·0	26·0
	E	—	—	—	—	—	—	68·1	7·350	53·0	25·0
		92·9	—	—	—	—	—	68·5	7·345	58·5	25·0
VN 5	R	98·0	7·410	32·5	21·5	0·70	0·09	90·2	7·370	38·5	22·0
	E	—	—	—	—	—	—	—	—	—	—
		97·2	7·440	30·0	22·5	1·30	0·12	—	—	—	—
VH 31	R	98·5	7·350	48·0	24·0	0·96	0·10	86·9	7·310	51·5	22·6
	E	—	—	—	—	1·43	0·11	—	—	—	—
		95·7	7·345	47·5	23·0	1·78	0·13	78·8	7·310	56·5	22·4
VH 32	R	98·6	7·370	44·0	23·8	0·86	0·09	90·0	7·335	50·0	23·3
	E	—	—	—	—	0·94	0·10	—	—	—	—
		97·5	7·385	36·5	22·0	1·22	0·09	83·2	7·345	52·5	23·8
VH 33	R	94·5	7·385	34·0	20·5	—	0·12	88·4	7·380	36·0	21·0
	E	—	7·380	38·5	22·0	—	0·12	68·4	7·335	46·0	22·0
		92·2	7·380	35·5	21·5	—	0·17	68·5	7·340	39·0	19·5
VE 62	R	91·8	7·425	33·0	23·0	0·97	0·07	77·6	7·400	36·0	22·0
	E	82·9	7·415	34·5	23·0	2·08	0·11	68·5	7·370	39·0	21·0
		85·0	7·410	33·0	22·0	1·57	0·12	63·5	7·375	38·5	21·0
VS 81	R	97·9	7·330	44·2	24·0	0·59	0·06	88·3	—	—	—
	E	—	—	—	—	0·84	0·07	—	—	—	—
		97·9	7·370	39·0	23·4	0·88	0·08	85·0	7·330	44·0	23·5
VS 82	R	96·0	7·440	42·0	27·0	0·68	0·11	82·8	—	—	—
	E	—	—	—	—	—	—	—	—	—	—
		92·0	7·455	37·0	26·0	1·50	0·12	71·7	—	—	—
PN 1	R	97·4	7·285	42·5	19·0	0·65	0·09	78·4	7·270	48·0	20·0
	E	—	—	—	—	1·20	0·11	—	—	—	—
		97·2	7·315	38·0	21·0	1·04	0·12	—	—	—	—

TABLE II—*continued*

Case No.		Arterial blood						Pulmonary arterial blood			
		So_2	*p*H	Pco_2 (mm.Hg)	Bicarb. (mEq/l.)	Lactate (mM/l.)	Pyruvate (mM/l.)	So_2	*p*H	Pco_2 (mm.Hg)	Bicarb. (mEq/l.)
PH 30	R	95·5	—	—	—	0·91	0·06	90·2	—	—	—
	E	—	—	—	—	—	—	78·6	—	—	—
		95·0	—	—	—	1·50	0·09	75·8	—	—	—
PE 65	R	93·5	7·415	38·0	24·0	0·53	0·07	—	—	—	—
	E	90·0	7·370	40·5	22·0	1·89	0·11	—	—	—	—
		89·9	7·360	38·0	20·0	2·54	0·12	—	—	—	—

Note: The first exercise sample was obtained in the 3rd and 4th minute, the second between the 8th and 10th minutes.
R, rest; E, exercise; So_2, oxygen saturation.

without septal defects, shown by crosses (Gazetopoulos *et al.*, 1966a). It is seen that the higher the ventilation, the lower the pulmonary arterial Pco_2.

It appears therefore that in these circumstances neither the arterial nor the venous blood chemistry exerts an influence on the ventilation.

Upright Exercise. Table III shows the findings in subjects exercised in the upright position on the bicycle ergometer with stepwise increases in load. Fig. 9 illustrates the main parameters studied: in the lower part the ventilation and heart-rate in the steady state are shown, the normal limits (Davies

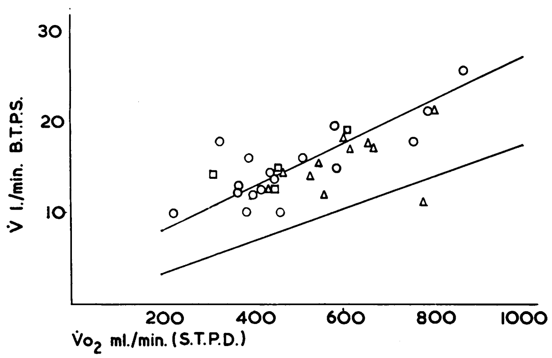

FIG. 1.—Ventilation ana oxygen uptake during exercise in the supine position at cardiac catheterization. The normal limits are shown. ○ atrial septal defect; △ ventricular septal defect; □ patent ductus arteriosus.

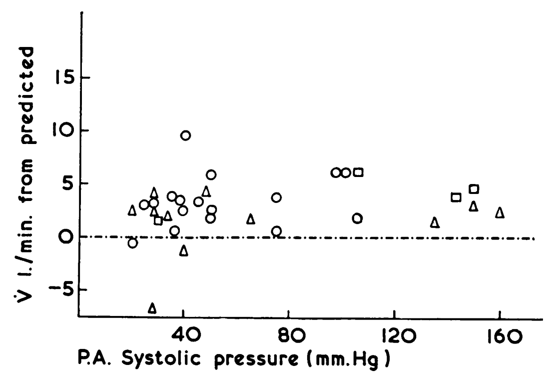

FIG. 2.—Ventilation during supine exercise expressed as deviation from the mean predicted normal for the given oxygen uptake, in relation to pulmonary arterial systolic pressure. Symbols as in Fig. 1.

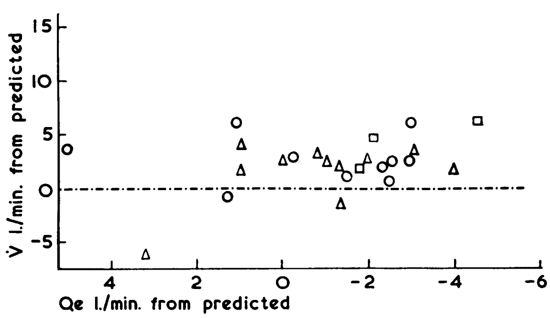

FIG. 3.—Excess ventilation in relation to the degree of impairment of cardiac output, expressed as deviation from the mean predicted for the given oxygen uptake. Symbols and definitions as in Fig. 1 and 2.

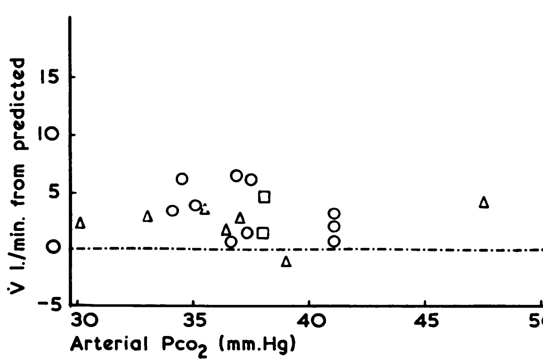

FIG. 4.—Excess ventilation and arterial Pco_2. Symbols and definitions as in Fig. 1 and 2.

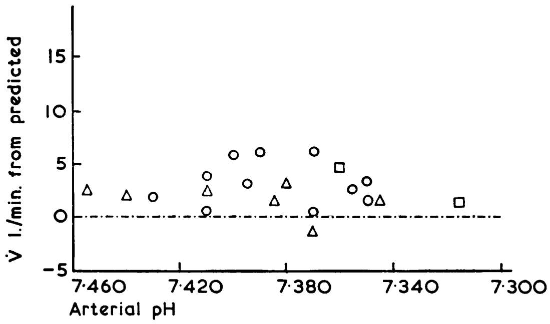

FIG. 5.—Excess ventilation and arterial *p*H. Symbols and definitions as in Fig. 1 and 2.

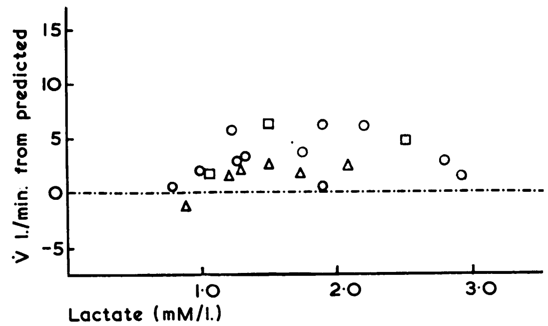

FIG. 6.—Excess ventilation and arterial lactate. Symbols and definitions as in Fig 1 and 2.

et al., 1965) being also indicated. Above them are given the *p*H, P_{CO_2}, oxygen saturation, and lactate concentration at the end of each 10-minute period. Four of the patients (Cases AN5, AH39, AH45, and VH 34) were able to perform at only lower levels (200–400 kpm./min.), and in all these dyspnœa

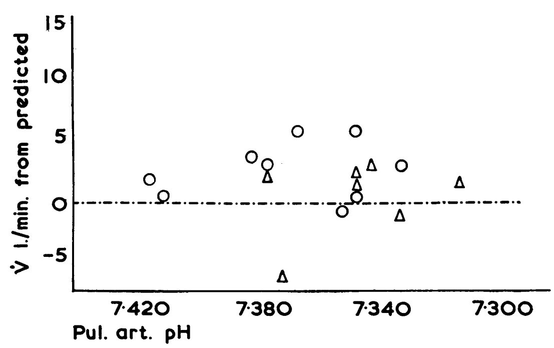

FIG. 7.—Excess ventilation and pulmonary arterial *p*H. Symbols and definitions as in Fig. 1 and 2.

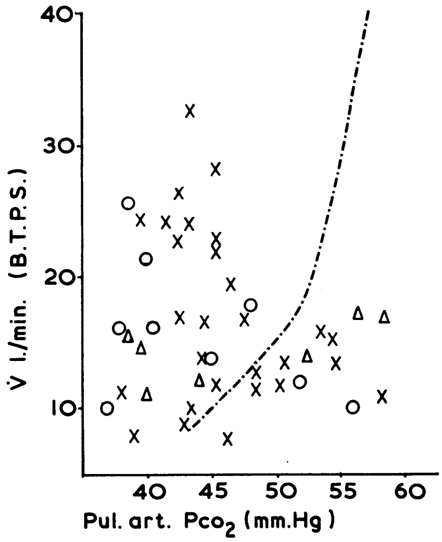

FIG. 8.—Ventilation and pulmonary arterial P_{CO_2}. Xs represent patients without septal defects (Gazetopoulos *et al.*, 1966a). Otherwise symbols as in Fig. 1. The broken line represents the normal V̇–mixed venous P_{CO_2} relationship from Riley *et al.* (1963). High ventilation is associated with lower values of P_{CO_2}.

was the limiting factor. Ventilation was excessive, and the blood chemistry showed changes consequent on hyperventilation. In two of them (Cases AH45 and VH32) raised pulmonary venous pressure could have been a stimulus to ventilation but in the other two it was normal. Both these patients (Cases AN5 and AH39) showed severe respiratory embarrassment after surgery, as a result of which they died. We have at present no explanation for this.

The other patients were able to reach higher exercise loads, and in many of them fatigue rather than dyspnœa appeared to be the limiting factor while hyperventilation was less obvious or not present. We note that some patients with high pulmonary arterial pressure and increased pulmonary blood flow were able to reach moderate exercise loads (600 kpm./min.) without impressive hyperventilation. Direct measurements of pressure and flow during upright exercise were not made by us, but the evidence of Bruce and John (1957) suggests that the upright posture does not lead to diminution in pulmonary flow or pressure in such patients, and the findings during supine exercise may reasonably be applied also in the upright position. Pulmonary plæonæmia and hypertension would, therefore, not appear to be essential primary determinants of hyperventilation, even up to maximal exercise tolerance. In all

TABLE III

FINDINGS BEFORE AND DURING EXERCISE IN THE UPRIGHT POSITION WITH STEPWISE INCREASE OF LOAD

Case No.		Exercise load (kpm./min.)	Oxygen uptake (ml./min.) STPD	Heart rate	Ventilation (l./min.) BTPS	Arterial blood					
						So_2	*p*H	Pco_2 (mm.Hg)	Bicarb. (mEq/l.)	Lactate (mM/l.)	Pyruvate (mM/l.)
VS 83	R	0	306	84	8·5	97·0	7·455	40·9	27·0	0·98	0·10
	Ex.	200	780	112	15·0	—	7·440	42·0	27·0	2·01	0·12
						96·5	7·445	41·0	26·5	1·95	0·13
		400	1050	120	21·5	—	7·440	39·0	25·5	2·15	0·14
						98·5	7·435	36·0	24·5	2·47	0·15
		600	1300	144	29·0	—	7·425	34·0	24·5	3·64	0·14
						97·0	7·395	40·0	23·5	5·20	0·19
		800	1700	164	34·0	97·2	7·415	38·0	24·0	6·90	0·19
						97·0	7·410	36·0	23·0	7·55	0·19
	Rec. (5′)		—	108	—	97·0	7·400	36·0	22·0	6·20	0·26
	(10′)		—	104	—	—	7·455	34·0	24·5	5·65	0·25
AS 82	R	0	—	86	9·3	97·0	7·420	36·2	23·0	0·65	0·09
	Ex.	200	—	108	19·5	—	—	—	—	—	—
						97·0	7·415	34·0	22·0	1·43	0·12
						97·0	7·415	34·0	22·0	1·43	0·12
		400	—	115	28·2	—	7·410	35·5	22·0	1·69	0·13
						96·5	7·415	34·0	22·0	2·02	0·14
		600	—	126	35·8	—	7·420	34·0	22 5	1·56	0·14
						96·5	7·420	33·5	22·0	2·08	0·14
		800	—	160	49·4	—	7·420	35·0	22·0	2·34	0·16
						96·5	7·410	30·0	20·0	2·86	0·18
		1000	—	175	—	96·5	7·360	26·5	17·0	8·13	0·26
						—	—	—	—	—	—
	Rec. (5′)		—	130	13·9	—	—	—	—	5·07	—
	(15′)		—	107	—	—	7·420	34·0	22·0	1·36	—
PH 30	R	0	200	96	4·0	—	7·420	34·0	22·5	0·65	0·07
	Ex.	200	560	104	13·4	—	—	—	—	—	—
						—	7·450	32·5	23·0	1·04	0·08
		400	1025	140	21·0	—	7·400	34·5	22·0	2·21	0·11
						—	7·410	33·0	22·0	2·03	0·13
		600	—	160	—	—	7·430	32·5	22·5	2·37	0·12
AH 45	R	0	256	80	6·1	98·0	7·485	30·5	23·0	1·36	0·06
	Ex.	200	660	156	19·6	—	7·500	27·5	22·0	1·75	0·09
						97·6	7·450	24·5	19·0	6·37	0·13
		400	—	180	34·2	—	7·445	23·5	19·5	5·46	0·16
						98·0	7·500	19·5	18·0	7·54	0·17
	Rec. (5′)		—	112	6·3	—	7·420	26·0	18·5	5·85	—
	(15′)		—	96	4·9	—	7·440	26·0	19,5	4·55	—
AH 39	R	0	265	80	12·2	94·0	7·525	34·5	28·5	0·85	0·07
	Ex.	200	750	128	22·8	—	7·500	34·0	27·5	1·69	0·10
						96·2	7·500	36·0	28·0	1·95	0·12
		400	1150	156	30·8	—	7·495	33·0	26·0	2·86	0·12
						92·0	7·485	34·0	26·0	3·38	0·13
	Rec. (5′)	—	—	100	15·1	—	7·485	32·0	25·0	2·47	0·15
	(10′)	—	—	100	11·0	96·0	7·520	30·0	26·0	1·95	0·13
VH 34	R	0	254	88	13·6	94·9	7·430	35·0	24·0	1·06	0·08
	Ex.	200	550	124	30·6	96·7	7·420	33·0	23·0	1·23	0·08
						95·0	7·415	35·0	23·0	1·50	0·10
AH 41	R	0	310	76	7·9	95·8	7·495	35·0	27·5	1·10	0·11
	Ex.	200	750	100	15·4	97·4	7·465	33·0	25·0	2·20	0·13
						96·4	7·445	36·0	25·0	2·46	0·16
		400	1205	124	22·0	97·5	7·435	35·5	24·0	2·46	0·18
						97·4	7·425	37·0	24·0	3·64	0·19
		600	1510	144	33·0	96·0	7·375	39·5	22·5	3·70	0·22
						96·0	7·405	31·0	21·0	5·45	0·22
	Rec. (5′)		—	88	8·9	—	7·450	30·0	22·5	—	—
VH 33	R	0	347	76	6·6	98·7	7·435	37·0	24·5	—	0·08
	Ex.	200	710	126	18·1	95·9	7·435	37·0	24·5	—	0·11
						95·9	7·430	31·0	22·5	—	0·12
		400	1055	144	21·0	94·8	7·425	37·0	24·0	—	0·14
						88·4	7·385	35·5	21·5	—	0·14
		600	1390	180	32·0	79·6	7·395	33·5	21·0	—	0·15
						77·3	7·375	32·0	19·5	—	—

TABLE III—*continued*

Case No.		Exercise load (kpm./min.)	Oxygen uptake (ml./min.) STPD	Heart rate	Ventilation (l./min.) BTPS	Arterial blood					
						So_2	*p*H	Pco_2 (mm.Hg)	Bicarb. (mEq/l.)	Lactate (mM/l.)	Pyruvate (mM/l.)
AN 8	R	0	250	88	10·0	96·0	7·530	28·0	24·5	1·11	0·06
	Ex.	200	755	110	19·0	—	7·540	27·0	24·0	1·82	—
						94·0	7·470	32·0	23·0	1·63	—
		400	1050	140	24·8	—	—	—	—	—	—
						95·0	7·450	33·0	23·0	2·08	0·08
		600	—	156	36·0	—	—	—	—	—	—
						96·0	7·430	34·0	22·0	2·80	0·14
	Rec. (5′)		—	100	—	96·0	7·475	27·0	21·5	—	—
AN 5	R	0	224	104	8·2	98·0	7·455	40·0	27·0	0·78	0·08
	Ex.	200	955	150	29·0	98·0	7·465	33·5	25·5	2·28	0·13
						98·0	7·495	33·5	27·0	1·69	0·12
	Rec. (10′)		—	—	—	98·0	7·475	37·0	27·0	1·04	0·10
	(20′)		—	—	—	96·5	7·490	35·0	27·0	0·98	0·09

Kpm. = kilopond metre; Rec.=recovery. Symbols otherwise as in Tables I and II.

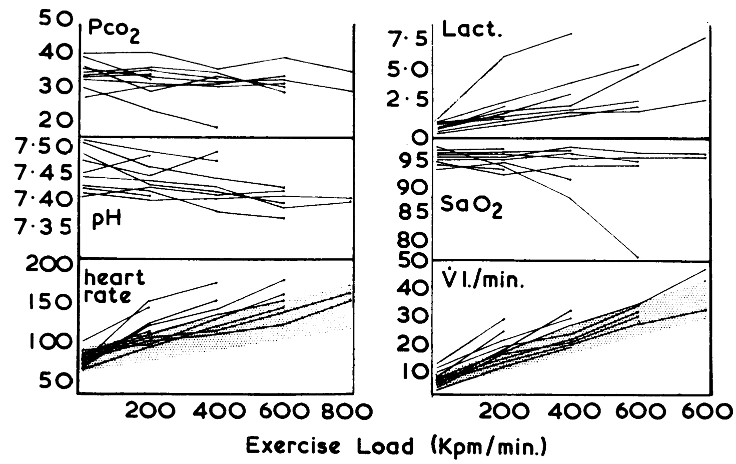

FIG. 9.—Ventilation, heart-rate, and blood chemistry during exercise in the upright position with stepwise increase in load. The normal ranges are shown by the shaded areas (Davies *et al.*, 1966). Excessive ventilation is often seen, and the blood chemistry changes as a result of this.

cases except one (Case VH33) the oxygen saturation remained normal; in the exception the ventilatory response was not unusual. The arterial lactate concentration was excessive in some patients and so were the lactate/pyruvate ratios.

In Fig. 10 we have plotted the lactate/pyruvate ratios and the excess ventilation in all patients whose oxygen uptake was less than 1200 ml./min. in this study, in both upright and supine positions. We have included for comparison the mean response of patients with pulmonary stenosis (solid line) and mitral stenosis (broken line) in whom similar studies were performed. The patients with left-to-right shunts show a variable response, but most cases behave in a manner similar to that of patients with pulmonary stenosis. The significance of this will be discussed later.

DISCUSSION

Uncertainty remains in the understanding of the control of ventilation on exercise in normal subjects, as evidenced by the number of recent symposia devoted to the topic. *A fortiori* the subject is more difficult to unravel in heart disease because of the complexity and interaction of the factors operating. This is particularly the case in patients with left-to-right shunts, in whom pulmonary hypertension, heart failure, lung damage, and impairment of systemic flow may coexist, each being a potential determinant of hyperventilation.

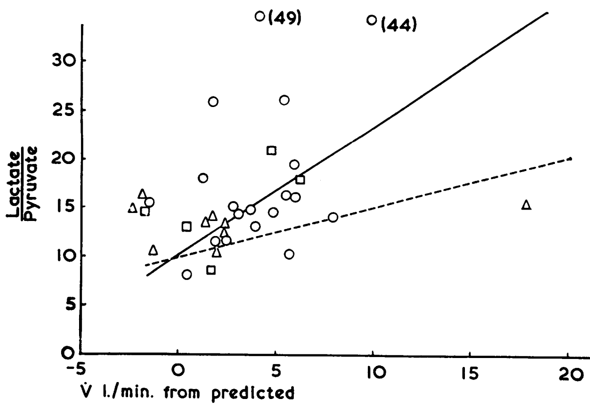

Fig. 10.—Lactate/pyruvate ratio and excess ventilation in all patients with oxygen uptakes below 1200 ml./min. The mean response of patients with pulmonary stenosis (solid line) and mitral stenosis (broken line), studied by similar techniques (Gazetopoulos *et al.*, 1966a) is shown for comparison. Symbols and definitions as in Fig. 1 and 2. For discussion see text.

Simultaneous measurement of a number of variables and the comparison of different disease groups may help towards better comprehension, but the problem remains complicated.

Pulmonary plæonæmia of considerable degree may be present in patients with left-to-right shunts without any symptoms whatsoever and with a demonstrably normal ventilatory response to exercise (e.g. Cases AN4, AN6, VN3). Sometimes, however, hyperventilation is observed on effort even in the absence of pulmonary hypertension (i.e. Case AN7). When pulmonary hypertension supervenes in patients with left-to-right shunts, symptoms are usually present, and hyperventilation is frequently, though not invariably, observed on effort (Cases AH44, AH45, PH30). It does not appear from our studies that pulmonary hypertension *per se* is an important direct causal factor in hyperventilation, and patients are often seen in whom severe pulmonary hypertension is associated with a normal ventilatory response to exercise (Cases AH41, AH43, VH32). A similar conclusion was drawn from similar studies in other forms of heart disease (Gazetopoulos *et al.*, 1966b).

In these studies, therefore, the pattern of ventilatory response to supine exercise has been variable but neither high flow nor pulmonary arterial pressure appear to be powerful independent determinants of hyperventilation. The same variability of response is seen also in upright exercise (Table III).

The influence of pulmonary venous hypertension on the ventilation has been discussed elsewhere (Gazetopoulos *et al.*, 1966b); increase of left atrial pressure has been found in a minority of patients in this study. In atrial septal defect this is a usual accompaniment of coexisting mitral valve disease or of failure of either ventricle. In ventricular septal defect or patent ductus arteriosus, the presence of mitral stenosis or of left ventricular failure leads to pulmonary venous hypertension. In two of our patients (Cases AH45 and VH34) the increase of left atrial pressure was considerable and both showed marked hyperventilation. Usually, however, the pulmonary venous pressure remains low in patients with septal defects at rest and on effort (Jönsson, Linderholm, and Pinardi, 1957; Stephens, Shafter, and Bliss, 1964) and only exceptionally would the pulmonary venous pressure appear to provide a significant ventilatory stimulus.

Impairment of systemic output has been proposed as a stimulus to ventilation (McIlroy, 1959), but various authors (Cotes, 1955; Arnott, 1963; Sloman and Gandevia, 1964) as well as ourselves (Gazetopoulos *et al.*, 1966b) have failed to find a satisfactorily demonstrable relation between this and the ventilation in different forms of heart disease. The same is true in the present group (Fig. 5). It has been suggested (Gazetopoulos *et al.*, 1966a) that there may be mechanisms of adaptation at tissue level to inadequate oxygen supply, and examination of the consequences of deficient cardiac output, such as the lactate/pyruvate ratio, could be more reliable indices of tissue hypoxia. A general relationship was found in those studies between this ratio and the ventilation: in isolated low output states, such as pulmonary valve stenosis, higher lactate/pyruvate ratios were seen at comparable degrees of hyperventilation than in patients with pulmonary venous congestion where a more powerful stimulus to ventilation lies in the lung. Most of our patients with left-to-right shunts show a pattern of response in this respect similar to patients with pulmonary stenosis (Fig. 12), suggesting some mechanism connected with tissue hypoxia rather than one related to the lungs in contributing towards hyperventilation in a number of these cases.

The arterial and venous blood gases, as in patients with other types of heart disease discussed elsewhere (Gazetopoulos *et al.*, 1966b), change mainly as a consequence of hyperventilation: the arterial P_{CO_2} may, however, be a fallible index of hyperventilation in these patients owing to coexisting lung disease. Only in severe cyanotic congenital heart disease have we seen variations of blood gases in such a manner as to stimulate ventilation.

We have been impressed with the variability of response to exercise on the part of these patients, and have found it difficult to discern which particular factors determine any one individual's response. Of those that are known to encourage hyperventilation, we have seen in this group evidence, in a few cases, of pulmonary venous hypertension and a response similar to that of patients with mitral stenosis. There has been evidence of an impaired cardiac output and resulting tissue hypoxia with a ventilatory response similar to that of patients with pulmonary stenosis. Excessive ventilation not explicable by these manifestations has, however, been observed. We note moreover that dyspnœa has been present without much hyperventilation in some cases.

One major factor which is missing for these considerations is that of organic lung damage and derangement of pulmonary function. This is likely to be a potent factor in symptomatology, and will be discussed in a subsequent paper.

Summary

Ventilatory, hæmodynamic, and metabolic studies have been performed at rest and during exercise in 34 patients with left-to-right shunts. Most patients showed an excessive ventilatory response to exercise, but this was not apparently related directly to the level of pulmonary arterial pressure or the magnitude of the pulmonary flow. In a minority of patients pulmonary venous hypertension was probably a stimulus to the ventilation.

No particular hæmodynamic parameter or combination of parameters can thus be shown to be directly associated with the manifest hyperventilation of patients with left-to-right shunts, and the cause of this must therefore be sought elsewhere.

The blood gases changed in a manner consequent upon the ventilation. The arterial lactate concentration was excessive in most patients showing hyperventilation, and the possible relation between tissue hypoxia and the ventilatory response has been discussed.

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